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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	27

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/349,925	CHANGEUX ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-47 and 51-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-47,51,52 and 55-62* is/are rejected.

7)☒ Claim(s) *53 and 54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment received on 12/13/02 has been entered. Claims 40-41, 46-47, 51, 54-56, 58-60 and 62 have been amended. Claims 40-47 and 51-62 are pending and are under current consideration.

Information Disclosure Statement

The IDS received on 10/03/00 has been considered.

Drawings

The drawings submitted on 12/13/02 have been approved.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-47, 51-52, 55-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse to the extent that the heterologous polypeptide is encoded by reporter gene, does not reasonably provide enablement for all other transgenic mice embraced by the claims. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous rejection is maintained for the reasons of record advanced on pages 3-11 of the Office action mailed on 7/25/02.

Applicant's arguments filed on 12/13/02 have been fully considered but are not found persuasive. Applicants argue that the phenotype resulting from expression of an oncogene is not unpredictable. In support of their arguments Applicants continue to argue that the promoter sequence embraced by the claims can direct expression of a reporter gene in the neurons of a transgenic mouse, wherein the pattern of expression of the reporter gene is consistent with the normal expression pattern of a β2-subunit of the neuronal nicotinic acetylcholine receptor. Applicants further maintain that the prior art made of record discloses numerous examples of transgenic mice where sequences encoding oncogenic proteins where linked to various promoter and/or enhancer elements, resulting in tissue-specific expression and tumor formation. For example, see Kioussis and Gordon. See pages 7-8 of the amendment.

In response, the Examiner maintains that the phenotype resulting from expression of an oncogene in a transgenic mouse is unpredictable. The desired phenotype appears to be tumor formation however, the guidance provided by the instant specification has failed to provide a correlation between expression of an oncogene and tumor formation in a transgenic mouse. While the working examples provided by the specification have detailed the creation of transgenic mice expressing a reporter gene, the working examples provided by the specification have failed to provide

a correlation between expression of an oncogene and tumor formation in a transgenic mouse. As such it appears that the guidance provided by the evidence of record has failed to overcome the unpredictability of the transgenic art with respect to a phenotype resulting from expression of a transgene. The Examiner maintains that the Kioussis and Gordon references provided by Applicants, while teaching that some transgenic mice comprising tissue-specific tumors have been created, do not establish that creating such mice is predictable. Kioussis, for example, discusses tumor formation in transgenic mice expressing oncogenes and reports that "expression of a transgene in a tissue usually does not guarantee generation of tumors". See page 202 of Kioussis at the bottom. Gordon, as Kioussis, discusses tumor formation in transgenic mice expressing oncogenes but does not suggest any degree of predictability with respect to tumor formation in transgenic mice expressing oncogenes. Gordon reports that not all tissues expressing the SV 40 T antigen in a transgenic mouse developed tumors suggesting a tissue tropism for the T antigen. Gordon goes on to report that expression of the polyomavirus large T antigen in transgenic mice does not result in tumor formation while transgenic expressing the middle-T oncogene develop vascular endothelial tumors. Gordon further suggests that the mechanism for tumor formation in such transgenic mice may be a "two-hit" mechanism as tumors in mice expressing SV40 large T and myc arise rarely among either a group of hyperplastic cells or normal cells. See pages 200-204 of Gordon. In light of such, it is maintained that Kioussis and Gordon do not provide sufficient evidence to overcome the unpredictability of the transgenic art. In addition, the enabled scope of the invention is a transgenic mouse

expressing a reporter gene. However, the evidence of record has failed to provide a correlation between expression of a reporter gene in the neurons of a transgenic mouse and expression of an oncogene in the neurons of a transgenic mouse such that a tumor predictably forms. Accordingly, it is maintained that expression of an oncogene in a transgenic mouse is unpredictable. See pages 5-7 and 8-9 of the Office action mailed on 7/25/02 and also Palmiter, Kappel and Cameron on page 6 of the Office action mailed on 7/25/02 which generally discuss the unpredictability of transgenic art.

Applicants continue to argue that a skilled artisan can routinely screen to determine those that express the transgene at a level sufficient to induce tumor formation and point to the *In re Wands* case law for support. Applicants submit that some necessary experimentation does not preclude enablement. See pages 8-10 of the amendment.

In response, the Examiner maintains that screening of transgenic mice to find one that exhibits a desired phenotype is welcoming trial and error experimentation to overcome the unpredictability of the transgenic art. A Wands analysis as presented on pages 6-7 of the Office action mailed on 7/25/02 suggests that the transgenic art is unpredictable and that such unpredictability may not be overcome by routine screening. Furthermore, the Kioussis and Gordon references as discussed in the preceding paragraph provide additional evidence that expression of an oncogene in a transgenic mouse does not routinely result in tumor formation.

With respect to the state of the prior art, Applicants continue to argue that Kioussis and Gordon provide evidence that tumor formation in transgenic mice expressing an oncogene is predictable. See page 10-12 of the amendment.

In response, the Examiner asserts that Kioussis and Gordon fail to provide sufficient evidence to overcome the unpredictability of the transgenic art, with respect to tumor formation in transgenic mice expressing an oncogene. See Kioussis and Gordon as discussed above and also on pages 8-9 of the Office action mailed on 7/25/02.

With respect to the breadth of the claims, Applicants have asserted that oncogenic sequences were well known in the art and available for use in the context of the claimed invention. See pages 12-13 of the amendment.

In response, the Examiner asserts that the issue is not whether the sequences of oncogenes are known. It appears that the issue is the phenotype resulting from expression of oncogenes. The claims broadly encompass all oncogenes, but the evidence of record has not supported any phenotype, particularly tumor formation, resulting from expression of a single oncogene in a transgenic mouse. Moreover, Kioussis and Gordon as discussed above have suggested that expression of different oncogenes may result in different phenotypes and that tumor formation may not predictably occur in all tissues that express an oncogene. See page 5 of the Office action mailed on 7/25/02.

With respect to the existence of working examples, Applicants assert that the specification has provided working examples that correlate to the expression of a reporter gene in a transgenic mouse. Applicants further assert that in view of the

working example the skilled artisan could successfully substitute an oncogene for a reporter gene. Applicants again argue that tumor formation in transgenic mice expressing an oncogene is predictable and again point to Kioussis and Gordon for support. See pages 13-14 of the amendment.

In response, the Examiner asserts that the issue at hand does not relate to physical substitution of a reporter gene for an oncogene, which should be routine in the field of molecular biology. The issue again boils down to whether tumors predictably form in transgenic mice expressing an oncogene, which is why the exemplified working example directed to a reporter gene does not correlate to the claimed invention. The Examiner maintains a level of unpredictability exists to that end as discussed above and also in the previous Office action. Kioussis and Gordon have suggested that expression of different oncogenes may result in different phenotypes and that tumor formation may not predictably occur in all tissues that express an oncogene as discussed above.

With respect to the amount of direction provided by the inventor Applicants assert that the instant specification has provided adequate guidance to enable the claimed invention. In particular, Applicants point to the working example directed to expression of a reporter gene in the neurons of a transgenic mouse. Applicants continue to argue that prior art references Kioussis and Gordon provide guidance with respect to expression of oncogenes in transgenic mice. Applicants assert that the instant specification does not need to disclose what is well known in the art. See page 15 of the amendment.

In response, the Examiner maintains that the instant specification has failed to provide guidance that correlates expression of an oncogene in the neurons of a transgenic mouse such that a tumor forms as previously discussed. It is further maintained, as discussed above, that the working example directed to expression of a reporter gene in neurons of a transgenic mouse does not correlate to expression of an oncogene that results in tumor formation in the neurons of a transgenic mouse due to the unpredictability of tumor formation in the transgenic art (see above). The Examiner asserts that Kioussis and Gordon do not provide sufficient evidence that expression of an oncogene resulting in tumor formation in the context of a transgenic mouse is predictable. In fact it appears as if Kioussis and Gordon have suggested a level of unpredictability, with respect to tumor formation resulting from oncogene expression in transgenic mice, exists in the art as discussed above.

With respect to the level of predictability in the art, Applicants assert that for the reasons of record including the prior art of record (Kioussis and Gordon) expression of oncogenes in transgenic mice predictably leads to tumor formation. See pages 15-16 of the amendment.

In response, the Examiner maintains expression of oncogenes in transgenic mice does not predictably lead to tumor formation as discussed in the preceding paragraphs and for the reasons previously made of record.

With respect to the level of skill in the art, Applicants have noted that the level of skill in the art was high at the time of Applicants' invention. See page 16 of the amendment.

In response, the Examiner acknowledges that the level of skill in the art may have been high at the time of Applicants' invention. However, as previously discussed the evidence of record has not provided adequate guidance, which correlates the expression of an oncogene with tumor formation in the context of a transgenic mouse, that overcomes the unpredictability of tumor formation in the transgenic art.

With respect to the quantity of experimentation needed to make or use the invention based on the content of the disclosure, Applicants assert that the specification has provided teachings with respect to making and using the transgenic mice of the claimed invention. In particular, Applicants assert that all that is necessary is substitution of an oncogene for a reporter gene and routine screening to identify the transgenic mice that develop tumors. See page 16 of the amendment.

In response, the Examiner asserts that as discussed above the evidence of record has not provided adequate guidance that correlates expression of an oncogene with tumor formation in a transgenic mouse. As discussed above, the transgenic art is unpredictable with respect to a phenotype resulting from transgene expression, in particular with respect to tumor formation resulting from expression of an oncogene. Finally, as discussed above, routine screening of transgenic mice to identify one exhibiting a desired phenotype is not sufficient to overcome the unpredictability of the transgenic art and undue experimentation required to make and use the claimed invention as set forth by the Wands analysis above and also on pages 6-7 of the Office action mailed on 7/25/02.

Applicants point out amended claims 40, 41, 55 and 59 no longer recite "that the DNA sequence is introduced into a mouse at an embryonic stage". Therefore, Applicants submit that the relevant aspect of the enablement be withdrawn.

In response, the Examiner acknowledges that claims 40, 41, and 59 no longer recite that the DNA sequence is introduced into a mouse at an embryonic stage. The relevant aspect of the rejection directed to DNA introduced into a mouse at an embryonic stage is withdrawn from claims 40, 41 and 59 (and from the claims that depend therefrom). Claim 55 however still recites introducing a DNA sequence into a mouse at an embryonic stage. As such the rejection of record over introduction of DNA into a mouse at an embryonic stage still applies to claim 55.

Accordingly, the rejection is maintained for the reasons of record and as discussed in the preceding paragraphs.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejections of claims 40-47 and 51-62 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been withdrawn.

Double Patenting

The previous doubling patenting rejection has been withdrawn in view of the entry of the terminal disclaimer filed on 1213/02 into the record.

Terminal Disclaimer

The terminal disclaimer filed on 12/13/02 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 6,452,066 (08/465,712) has been reviewed and is accepted. The terminal disclaimer has been recorded.

Allowable Subject Matter

Claims 53-54 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.
Art Unit 1632

PETER PARAS
PATENT EXAMINER